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OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, P.C. 1940 DUKE STREET ALEXANDRIA, VA 22314				
EXAMINER				
CUTLIFF, YATE KAI RENE				
ART UNIT		PAPER NUMBER		
1621				
NOTIFICATION DATE		DELIVERY MODE		
11/07/2008		ELECTRONIC		

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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### Office Action Summary

**Application No.**

10/578,783

**Applicant(s)**

ARRIGHI ET AL.

**Examiner**

YATE' K. CUTLIFF

**Art Unit**

1621

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 05 August 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-25 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-25 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SF/ICE)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

**DETAILED ACTION**

***Status of Claims***

1. Claims 1 - 25 are pending.  
  
Claims 26 and 27 have been canceled  
  
Claims 1 - 25 are rejected.

***Claim Rejections - 35 USC § 103***

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

3. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
  2. Ascertaining the differences between the prior art and the claims at issue.
  3. Resolving the level of ordinary skill in the pertinent art.
  4. Considering objective evidence present in the application indicating obviousness or nonobviousness.
4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1 – 8, and 12 - 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fan W. et al. (CN 1297885, English translation) in view of Bromine Compounds, Ltd. (Bromine) (WO 03/002517), and further in view of Shavel, et al. (US 3,007,940).

6. Rejected claim 1 cover, inter alia, a process for the synthesis of gabapentin comprising the preparation of 1,1-cyclohexanediactic acid monoamide, the Hofmann transposition of the same monoamide, the purification of a gabapentin salt and the crystallization from organic solvent, wherein the preparation of the acid monoamide comprises: a) the amination of 1,1-cyclohexanediactic acid anhydride by reaction with aqueous  $\text{NH}_3$  at a temperature lower than  $30^\circ\text{C}$  by using a  $\text{NH}_3$ /anhydride molar ratio lower than 3; b) the product precipitation through the acidification of the reaction mixture, wherein the 1,1-cyclohexanediactic acid monoamide is not crystallized.

Rejected claim 15 teaches the process for the preparation of 1,1-cyclohexanediactic acid monoamide (acid monoamide or CHDAAM), which comprises: a) the amination of 1, 1-cyclohexanediactic acid anhydride by reaction with aqueous  $\text{NH}_3$  at a temperature lower than  $30^\circ\text{C}$  by using a  $\text{NH}_3$ /anhydride molar ratio lower than 3; b) the product precipitation through the acidification of the reaction mixture, wherein the 1,1- cyclohexanediactic acid monoamide is not crystallized.

Rejected claims 2, 3, 16, and 17 teach that the  $\text{NH}_3$  is in aqueous solutions of various concentration amounts. Rejected claims 4 and 18 teach the use of hydrochloric

acid in the acidification step, while rejected claims 5 and 19 teach the concentration amount. Rejected claims 6, 7, 20 and 21 teach the molar ratios for ammonia to 1,1-cyclohexanediactic acid anhydride. Rejected claims 8 and 22 teach the reaction temperature.

Rejected claims 12, 13, 14, 23, 24 and 25 teach a process for transforming 1,1-cyclohexanediactic acid into the corresponding anhydride, with or without the presence of an organic solvent.

7. Fan et al. teaches discloses a process for preparing 1,1-cyclohexanediactic acid monoamide by amination of 1,1-cyclohexanediactic acid anhydride at a temperature of 30-110°C. The process of Fan discloses the use of an organic solvent (methylbenzene) in its process of forming the acid monoamide. Additionally, Fan et al. teaches a molar ratio of 2.2-4, which is within the claimed molar ratio of lower than 3. (abstract). In Fan et al. the concentration of the ammonia in the aqueous solution is 28%. (see page 4, paragraph 3 of translation). Additionally, Fan discloses a process for the synthesis of the 1,1-cyclohexanediactic acid anhydride by the reaction of 1,1-cyclohexane diactic acid with acetic anhydride. (see page 6, step 3). Further, in the process taught in Preferred Embodiment 2 for preparing the 1,1-cyclohexanediactic acid monoamide, the 1,1-cyclohexanediactic acid anhydride is mixed with toluene prior to the addition of the ammonia water. The pH is adjusted down to 3 with concentrate sulfuric acid at a temperature of 60°C. A course 1,1-cyclohexanediactic acid monoamide product is produced and washed with water. (see pages 6 and 7).

Fan fails to disclose the following: that hydrochloric acid is used to lower the pH; that an organic solvent is used in the process for making the 1,1-cyclohexanediactic acid anhydride from the 1,1-cyclohexanediactic acid; animation of the 1,1-cyclohexanediactic acid anhydride is carried out at a temperature between 10 and 25°C.

However, Bromine, on page 2 discloses a reaction that produces 1,1-cyclohexanediactic acid monoamide by amination with ammonia in an aqueous solution, then the acidification of the reaction product with hydrochloric acid. Bromine teaches the same type of reaction where the reaction temperature is below 20°C, however, the  $\text{NH}_3$ /anhydride molar ratio is 5 to 10. (see page 3 paragraph 5). Additionally, neutralization (acidification to precipitate the 1,1 -cyclohexanediactic acid monoamide) is carried out with  $\text{H}_2\text{SO}_4$  and at a temperature below 30°C. (see page 5 paragraph 4). However, on page 4 of Bromine discloses that neutralization of the reaction mixture can be carried out with aqueous hydrochloric acid, and the acid monoamide precipitates when the solution is slightly acid. Further, according to Bromine the crystallization step is simply done to further purify the crude CHDAAM and thus not necessary. (see page 6, paragraph 2). In Bromine, prior to purification by crystallization, the crude CHDAAM resulting from the neutralizations stage is water washed to separate it from the slurry generated. (see page 6, 1st paragraph). Like Fan et al. Bromine states that the 1,1-cyclohexanediactic acid anhydride can be prepared by reacting 1,1-cyclohexanediactic acid with acetic anhydride.

Both Fan et al. and Bromine fail to disclose the use of an organic solvent in the preparation of the 1,1-cyclohexanediactic acid anhydride.

However, Shavel, et al. , in Example II at column 5, teaches the process for making cyclohexanediactic anhydride from cyclohexanediactic acid in a reaction with acetic anhydride and an organic solvent, i.e. petroleum ether and benzene.

The difference between the claimed invention and main references of Fan et al. and Bromine is the temperature and the molar ratio of  $\text{NH}_3$ /anhydride; the inclusion of a crystallization step to purify the crude 1,1-cyclohexanediactic acid monoamide; and the use of an organic solvent in the process for preparing the 1,1-cyclohexanediactic acid anhydride.

However, the references of Fan et al. and Bromine demonstrate that the temperature and the molar ratio of  $\text{NH}_3$ /anhydride ratio can vary within a great range without being detrimental to the reaction.

Further, change in temperature, concentration, or both, is not a patentable modification unless such changes produce new and unexpected result which is different in kind and not merely in degree from results of prior art. It is known from the disclosure of Fan et al. that a molar ratio lower than 3 has a positive affect in optimizing the yield of 1,1-cyclohexyl oxalic amide in the reaction. The skilled artisan would be motivated to change a result-effective variable. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454,456, 105 USPQ 233, 235 (CCPA 1955). In this instance, both prior art references amine 1,1-cyclohexanediactic acid

anhydride with  $\text{NH}_3$ . Applicant's claimed process discloses reaction parameters that overlap and fall within those of the Fan et al. and Bromine references. It is well-established that merely selecting proportions and ranges is not patentable absent a showing of criticality. In re Becket, 33 USPQ 33, (CCPA 1937). In re Russell, 439 F.2d 1228, 169 USPQ 426 (CCPA 1971). As such, Applicant's variations in temperature and molar variations are merely an optimization of range or other variable within the claims that flow from "normal desire of artisan to improve upon what is already known. Further, there is no evidence to indicate the claimed process obtains a greater purity than obtained by Bromine. Therefore, any chemist reading the prior art could logically assume that higher purity might be obtainable, and by experimentally varying the conditions of temperature and acidity could find the most productive conditions.

With regard to use of crystallization by both Fan and Bromine as an additional purification process, it is noted in Bromine that the process, as discussed, is not necessary. Fan et al., Bromine and Applicant water wash the crude CHDAAM precipitate of neutralization (with acid). The water washing by Applicant, would be understood by one skilled in the art can be deemed as a different means of further purification of Applicant's crude acid monoamide. Applicant's process merely eliminates the additional purification step of crystallization (or re-crystallization) of the crude acid monoamide, when by Applicant's own admission high purity is not required for transformation of the 1,1-cyclohexanediactic acid monoamide for production of gabapentin. (see page 2, lines 24 - 26). Omission of an element and its function is



obvious if the function of the element is not desired. Ex parte Wu, 10 USPQ 2031 (Bd. Pat. App. & Inter. 1989). MPEP 2144.04

With regard to the use of toluene as a solvent in the preparation of the 1,1-cyclohexanediactic acid anhydride, Shavel et al. use petroleum ether and benzene mixture which is a nonpolar organic solvent mixture. Toluene is a nonpolar organic solvent. Further, Applicant's use of toluene appears to be a mere change in the sequence of adding ingredients, since Fan et al. adds toluene in the process of their Embodiment 2. Specifically, it appears that some toluene remains in the reaction after the production of the 1,1-cyclohexanediactic acid anhydride and at the time the  $\text{NH}_3$ /anhydride is added. Applicant is reminded that selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results. In re Burhans, 154 F.2d 690, 69 USPQ 330 (CCPA 1946). Also, selection of any order of mixing ingredients is prima facie obvious. In re Gibson, 39 F.2d 975, 5 USPQ 230 (CCPA 1930).

8. Claim 9 – 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fan et al. (CN 1297885 (English translation) in view of Bromine Compounds, Ltd. (Bromine) (WO 03/002517).

9. Rejected claim 9 teaches a precipitation process of 1,1-cyclohexanediactic acid monoamide by acidification of the ammoniacal solution of the monoamide and where the 1,1-cyclohexanediactic acid monoamide is not crystallized. Rejected claim 10 disclosed the use of hydrochloric acid in the gaseous form, while rejected claim 11 teaches the concentration of the hydrochloric acid.

Fan et al. discloses a process for preparing 1,1-cyclohexanediactic acid monoamide by amination of 1,1-cyclohexanediactic acid anhydride at a temperature of 30-110°C. The acidification of the ammoniacal solution of Fan et al. occurs as the temperature is heated to 60°C and continues to adjust the pH down to 3. (see page 6 paragraph 4).

Fan et al. fails to disclose that the temperature is between 40 and 45° and that the desired pH end point is 3.8 to 4.2.

However, in Bromine the neutralization is carried out at a temperature below 30°C and reduces the pH of down to about 5, with the precipitation of the crude 1,1-cyclohexanediactic acid monoamide starting at pH 7-8, when the solution is slightly acid. (see page 4 paragraph 4, & page 5 last 2 sentences). Further, on page 4 of Bromine discloses that neutralization of the reaction mixture can be carried out with aqueous hydrochloric acid, and the acid monoamide precipitates when the solution is slightly acid.

The difference between Applicant's claimed process and the process disclosed by Fan et al and Bromine; is that Applicant's acidification (neutralization) temperature ranges fall between the high range of Bromine and the mid range of Fan et al. Further, Applicant's pH end point falls between those of Fan et al. and Bromine.

In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976) Further, a prima facie case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one

skilled in the art would have expected them to have the same properties. Titanium Metals Corp. of America v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (Court held as proper a rejection of a claim directed to an alloy of "having 0.8% nickel, 0.3% molybdenum, up to 0.1% iron, balance titanium" as obvious over a reference disclosing alloys of 0.75% nickel, 0.25% molybdenum, balance titanium and 0.94% nickel, 0.31% molybdenum, balance titanium.). Applicant's claimed process is seeking to be distinguished from Fan et al. and Bromine by disclosing the median temperature and ranges at which the acid monoamide precipitates from the solution.

For the reasons set forth above in paragraph 9, It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to prepare the 1,1-cyclohexanediactic acid monoamide by precipitating the ammoniacal solution by varying the temperature ranges as suggested by Fan et al. and Bromine and continuing to add the acid until the desired pH is reached in the production of 1,1-cyclohexanediactic acid monoamide.

Therefore, all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. KSR International Co. v. Teleflex Inc., 550 U.S. \_\_\_, 82 USPQ2d 1385 (U.S. 2007).

### ***Response to Arguments***

10. Applicant's arguments filed August 5, 2008 have been fully considered but they are not persuasive.

11. Applicant respectfully asserts that their claimed process produces a product that has a high purity, not lower than 99%. However, this limitation is not claimed. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

12. Applicant respectfully asserts that absent the instant invention, there would be no reason for one of ordinary skill in the art to modify the teachings of Fan et al. or Bromine since neither process appears to be problematical. Applicant is reminded that "any judgement on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper." In re McLaughlin 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971).

13. Applicant respectfully asserts that the Examiner has simply engaged in picking and choosing temperatures and ratios which support the Examiner's position, and ignoring that the temperatures and ratios teach away from the present invention. In re Margaria, the court stated to rebut a case of prima facie obviousness the Applicant must establish the existence of unexpected properties in the range claimed or by showing that the art in any material respect taught away from the use of the carbon range claimed. In the instance case, Applicant's ranges either overlap or fall within the ranges of the claimed references and there has been no factual evidence presented to

show that the process, with the claimed ranges exhibit some superior property or advantage that a person of ordinary skill in the relevant art would have found as unexpected in the preparation of 1,1-cyclohexanediactic acid monoamide.

14. Applicant respectfully asserts that the process is not the product of routine experimentation because neither Fan et al. nor Bromine disclose avoiding a crystallization step. However, in Fan et al. the additional step is a re-crystallization step of the coarse 1,1-cyclohexanediactic acid monoamide which was obtained after washing with water. Omission of an element and its function is obvious if the function of the element is not desired. Ex parte Wu, 10 USPQ 2031 (Bd. Pat. App. & Inter. 1989).

MPEP 2144.04

15. Claims 1 - 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fan W. et al. (CN 1297885 (English translation) in view of Bromine Compounds, Ltd. (Bromine) (WO 03/002517), and further in view of Shavel, et al. (US 3,007,940), for the reasons set out in the Office Action mailed May 30, 2008; and as set out above.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to YATE' K. CUTLIFF whose telephone number is (571)272-9067. The examiner can normally be reached on M-TH 8:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Daniel M. Sullivan can be reached on (571) 272 - 0779. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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